Validation Study of the Proposed IASLC Staging Revisions of the T4 and M Non-small Cell Lung Cancer Descriptors Using Data from 23,583 Patients in the California Cancer Registry

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Background: We performed a validation study of the proposed International Association for the Study of Lung Cancer (IASLC) tumor, node, metastasis (TNM) and stage grouping revisions on advanced nonbronchioloalveolar carcinoma (non-BAC) non-small cell lung cancer (NSCLC).

Methods: Twenty-three thousand five hundred eighty-three patients from the California Cancer Registry between 1999 and 2003 with histologically confirmed non-BAC NSCLC and complete TNM staging were identified and reclassified according to the IASLC proposed TNM revisions and new stage groupings. Twelve thousand nine hundred one stage IIIB and IV patients formed the primary analysis of the changes to T4 and M descriptors. Surveillance, Epidemiology, and End Results extent of disease codes were used to identify various T4 and M descriptors. Cox proportional hazards regression was used to calculate hazard ratios (HRs) among the stage groupings of the current and proposed staging system with adjustment for ethnicity, gender, age, histology, histologic grade, socioeconomic status, surgery, radiation, and chemotherapy.

Results: The proposed changes to the T4 and M descriptors were supported by overall survival analysis. T4 due to additional nodules had significant survival advantage over other T4 and M descriptors among non-BAC NSCLC and individual histology and warrants down-staging to T3. Pericardial effusion had survival similar to M1b patients. Cox proportional hazards regression analysis supports subdividing M descriptor into M1a (versus IASLC stage IA; HR = 4.90; 95% confidence interval: 4.49–5.34) and M1b (versus IASLC stage IA; HR = 6.84; 95% confidence interval: 6.30–7.44).

Conclusions: IASLC has greatly improved the T4 and M descriptors allowing better prognostication of advanced non-BAC NSCLC. Pericardial effusion may be considered as M1b rather than M1a.

Key Words: IASLC lung cancer staging system, AJCC/UICC staging system, T4 descriptor, M descriptor, Non-small cell lung cancer, Survival, Pericardial effusion, California Cancer Registry.

(*J Thorac Oncol.* 2008;3: 216–227)

The current 6th edition of the Union Internationale Contre le Cancer (UICC6) staging system[1] for lung cancer has not been changed since the publication of the 5th edition in 1997.[2] Nevertheless, formal processes for continuous improvement of the tumor, node, metastasis (TNM) classification has been established since 2002.[3] A new proposed revision of the tumor (T),[4] nodes (N),[5] and metastasis (M)[6] descriptors for the forthcoming (7th edition) UICC lung cancer staging system has been recently proposed by the International Association for the Study of Lung Cancer (IASLC) after a rigorous study by an international panel using data from Europe, Asia, Australia, and North America. The proposed revision maintained the current N descriptors in the non-small cell lung cancer (NSCLC) staging system[5] but proposed several changes to the T descriptor.[4] For early stage T descriptor, one major revision was to subdivide T1 into T1a (≤2 cm) and T1b (>2 cm to 3 cm) and subdivide T2 into T2a (>3 cm to 5 cm), T2b (>5 cm to 7 cm), and T3 (>7 cm). For advanced T descriptors, one major revision is to reclassify T4 due to additional satellite nodules in the same lobe to T3 while

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Acknowledgment of Research Support: UCI Departments of Medicine, and Epidemiology.

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Presented in part at the 12th World Conference on Lung Cancer, Seoul, Korea, September 2–6, 2007.

Disclaimer: The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract N01-PC-35136 awarded to the Northern California Cancer Center, contract N01-PC-35139 awarded to the University of Southern California, and contract N01-PC-54404 awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement 1U58DP00807-01 awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred.

ISSN: 1556-0864/08/0303-0216

upstaging pleural dissemination (malignant pleural effusion/pleural nodules) and malignant pericardial effusion to M1a.[4] The major revision to the M descriptor is to subdivide it into M1a and M1b. "Contralateral intrapulmonary nodules" is grouped together with "malignant pleural dissemination" and "malignant pericardial effusion" into the new M1a category. All other distant metastasis will be grouped as M1b.[6] One of the proposed stage grouping changes is reclassifying the new T4N0-1M0 from stage IIIB as stage IIIA.[7] All these revisions and new grouping were internally validated and the Surveillance, Epidemiology, and End Results (SEER) database from 1998 to 2000 was used for external validation.[8]

We have previously shown that patients with T4 disease due to additional nodules in the same lobe and patients with M disease due to ipsilateral intrapulmonary nodules had better survival than T4 and M by other criteria respectively for both bronchioloalveolar carcinoma (BAC) and non-BAC NSCLC using SEER database.[9,10] We are thus interested in performing an external validation study of the IASLC proposed staging changes using the California Cancer Registry (CCR) database. Using CCR database we have previously published that patients with BAC had statistically improved survival after the publication of the World Health Organization (WHO) changes in the definition of BAC.[11] BAC also has unique clinicopathologic (more female, more nonsmokers, higher incidence of additional nodules in the same lobe, higher incidence of intrapulmonary metastasis) and molecular features (higher percentage of epidermal growth factor receptor mutations).[11–13] As such we have performed a separate validation study on these staging changes specifically to BAC using CCR.[14]

In this study, we adopted all the IASLC proposed changes to the T and M descriptors and reclassified all non-BAC NSCLC patients according to the new stage grouping and primarily analyzed survival differences due to the changes to the T4 and M descriptors. The 1999 WHO change in the definition of BAC[15] has changed the proportion and clinicopathologic features of BAC and adenocarcinoma[11,12] and may have been affected survival of other NSCLC histologies. Thus we analyzed patients diagnosed after 1998 (1999–2003) similar to how IASLC used the SEER database from 1998–2000 as the external validation set.[6]

PATIENTS AND METHODS

Objective

The primary outcome measure was to compare the stage-specific overall survival (OS) of advanced non-BAC NSCLC using current UICC6 staging system and the proposed IASLC staging modifications.

Population

A case-only analysis was conducted on incident NSCLC patients from CCR diagnosed between 1999 and 2003 who had complete TNM staging data and follow-up data. We limited the analysis to patients diagnosed after 1999, i.e., date of the WHO revised classification of lung tumors.[15] Data were abstracted from medical and laboratory records by trained tumor registrars according to Cancer Reporting in California: Vol. IV, Abstracting and Coding Procedures for Hospitals.[16]

Tumor site and histology were abstracted as previously described.[9–11] BAC histology was excluded, as we have separately performed a validation study for this histologic subtype.[14] Non-small cell histologies were categorized as undifferentiated NSCLC if they were not coded as adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or as a metastatic lung lesion from a separate primary tumor, as previously described.[9–11] Cytology specimens have been shown to be inaccurate in NSCLC diagnosis compared with histology specimens.[17] Thus, in an attempt to limit potential variability in histologic classification, only histologically confirmed NSCLC cases were analyzed. Patient demographic data were abstracted using SEER codes. The measurement of socioeconomic status used in this analysis was a composite measure using CCR and census data as previously described.[18,19] Radiation therapy and surgical techniques were abstracted using SEER codes. Chemotherapy given during the first course of therapy was ascertained using CCR codes.

For each patient in CCR, the Extent of Disease (EOD) coding variable was analyzed, to allow recoding into and comparison of the existing versus proposed revised staging system. EOD 65 which codes for "separate tumor nodule(s) in the same lobe," EOD 71 which codes for "heart, visceral pericardium," EOD 72 which codes for "malignant pleural effusions," EOD 73 which codes for "adjacent rib," EOD 75 which codes for "sternum, vertebra(e) skeletal muscle, skin of chest," EOD 77 which codes "separate tumor nodule(s) in separate lobe," EOD 78 which codes for "separate tumor nodule(s) in contralateral lung" and EOD 79 which codes for "(malignant) pericardial effusion" were used to identify the various T and M descriptors that were reclassified by IASLC. A total of 226 T3 patients with EOD 73 were reclassified as T4 according to the UICC6 staging system.

Restaging Patients According to the IASLC Revision for T4 and M Descriptors

Based on proposed IASLC revisions and stage grouping, the T4 descriptor for additional tumor nodules in the same lobe was changed to T3. We restaged these patients (T3N0M0) as stage IIB, patients with T3N1–2M0 as IIIA, and patients with T3N3M0 remained staged IIIB. The T4 descriptor for pleural dissemination (malignant pleural effusion/pleural nodules) was changed to M1a and so were patients with malignant pericardial effusion and we restaged these patients as stage IVA. The M descriptor for ipsilateral intrapulmonary nodules was changed to T4. These patients were staged according to the nodal status. Patients with contralateral intrapulmonary nodules were staged as M1a and grouped as stage IVA. Even though the proposed IASLC staging does not officially separate stage IV into stage IVA and stage IVB, we grouped stage IV patients into two groups according to M1a and M1b to facilitate Cox proportional regression analysis. We restaged all T4N0-1M0 patients as

TABLE 1. Clinicopathologic Features of non-BAC NSCLC Patients (N = 13,401) with UICC6 T4 and M Descriptors that Undergo Revisions as Proposed by IASLC

	UICC6 Stage IIIB				UICC6 Stage IV		
	T4-"Additional Nodules" (%)	T4-"Pleural Dissemination" (%)	T4-"Pericardial Effusion" (%)	T4-"Invasion" (%)	M-"Ipsilateral Pulmonary Nodules" (%)	M-"Contralateal Pulmonary Nodules" (%)	M- "Distant Metastasis" (%)
N	422	1773	320	1607	745	1148	6886
Mean age of diagnosis	67.9	69.6	66.1	66.0	67.4	68.6	65.1
(±SD)	±10.3	±11.5	±12.3	±11.0	±10.4	±11.3	±11.3
Gender							
Male	228 (54.0)	1033 (58.2)	168 (52.5)	952 (59.2)	404 (54.2)	627 (54.6)	3975 (57.7)
Female	194 (46.0)	740 (41.7)	152 (45.7)	655 (40.8)	341 (45.8)	521 (45.4)	2911 (42.3)
Race							
Caucasian	336 (79.6)	1243 (70.1)	231 (72.2)	1153 (71.8)	537 (72.1)	819 (71.3)	4888 (71.0)
African-American	31 (7.4)	146 (8.2)	22 (6.9)	159 (9.9)	67 (9.0)	84 (7.3)	630 (9.2)
Hispanic	26 (6.2)	206 (11.6)	36 (11.3)	138 (8.6)	77 (10.3)	120 (10.5)	703 (10.2)
Chinese	5 (1.2)	50 (2.8)	5 (1.6)	32 (2.0)	12 (1.6)	31 (2.7)	187 (2.7)
Non-Chinese Asian	23 (5.5)	123 (6.9)	23 (7.2)	120 (7.5)	51 (6.9)	89 (7.6)	451 (6.6)
Other	1 (0.2)	5 (0.3)	3 (0.9)	5 (0.3)	1 (0.1)	5 (0.4)	27 (0.4)
Socioeconomic status (SES)							
Quintile 1 (SES1-lowest)	58 (13.7)	339 (19.1)	58 (18.1)	242 (15.1)	120 (16.1)	177 (15.4)	1074 (15.6)
Quintile 2 (SES2)	83 (19.7)	383 (21.6)	65 (20.3)	318 (19.8)	138 (18.5)	245 (21.3)	1327 (19.3)
Quintile 3 (SES3)	98 (23.2)	390 (22.0)	82 (25.6)	378 (23.5)	173 (23.2)	254 (22.1)	1505 (21.9)
Quintile 4 (SES4)	92 (21.8)	360 (20.3)	59 (18.4)	345 (21.5)	156 (20.9)	241 (21.0)	1542 (22.4)
Quintile 5 (SES5-highest)	91 (21.6)	301 (17.0)	56 (17.5)	324 (20.2)	158 (21.2)	231 (20.1)	1438 (20.9)
Histology							
Adenocarcinoma	211 (50.0)	692 (39.0)	128 (40.0)	528 (32.9)	359 (48.2)	487 (42.4)	3173 (46.1)
Squamous cell carcinoma	97 (23.0)	503 (28.4)	85 (26.6)	571 (35.5)	196 (26.3)	290 (25.3)	1092 (15.9)
Large Cell carcinoma	19 (4.5)	111 (6.3)	25 (7.8)	74 (4.6)	28 (3.8)	64 (5.6)	440 (6.4)
Undifferentiated carcinoma	95 (22.5)	467 (26.3)	82 (25.6)	434 (27.0)	162 (21.7)	307 (26.7)	2181 (31.7)
Histologic grade							
Well-differentiated	29 (6.9)	49 (2.8)	11 (3.4)	37 (2.3)	37 (5.0)	48 (4.2)	115 (1.7)
Moderately-differentiated	92 (21.8)	254 (14.3)	32 (10.0)	264 (16.4)	146 (19.6)	184 (16.0)	726 (10.5)
Poorly-differentiated	197 (46.7)	733 (41.3)	128 (40.0)	715 (44.5)	297 (39.9)	405 (35.3)	2436 (35.4)
Un-differentiated	13 (3.1)	83 (4.7)	21 (6.6)	68 (4.2)	30 (4.0)	44 (3.8)	321 (4.7)
Unknown	91 (21.6)	654 (36.9)	128 (40.0)	523 (32.5)	235 (31.5)	467 (40.7)	3288 (47.7)
Surgery							
Yes	245 (58.1)	124 (7.0)	13 (4.1)	366 (22.8)	231 (31.0)	89 (7.8)	395 (5.7)
No	177 (41.9)	1649 (93.0)	307 (95.9)	1241 (77.2)	514 (69.0)	1059 (92.2)	6487 (94.2)
Unknown	0 (0.0)	0. (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Radiation							
Yes	159 (37.7)	660 (37.2)	122 (38.1)	1081 (67.3)	266 (35.7)	334 (29.1)	3852 (55.9)
No	263 (62.3)	1113 (62.8)	198 (61.9)	526 (32.7)	479 (64.3)	814 (70.9)	3034 (44.1)
Chemotherapy							
Yes	155 (36.7)	711 (40.1)	155 (48.4)	960 (59.7)	336 (45.1)	549 (47.8)	3141 (45.6)
No	261 (61.8)	999 (56.3)	154 (48.1)	600 (37.3)	387 (51.9)	562 (49.0)	3524 (51.2)
Unknown	6 (1.4)	63 (3.6)	11 (3.4)	47 (2.9)	22 (3.0)	36 (3.1)	221 (3.2)

stage IIIA (which represents a major change in the current proposed IASLC stage grouping).[7]

All early stage tumors were also reclassified according to their tumor sizes and EOD codes and their stage grouping according to the UICC6 and IASLC proposed changes for the Cox proportional regression analysis.

Statistical Analyses

Comparisons of demographic, clinical, and pathologic variables were made for NSCLC patients, using Pearson χ^2 statistic or Fisher exact test for nominal variables and Student t test for continuous variables. Analysis of variance with Tukey's posthoc test was used for multi-

TABLE 2. Survival Characteristics of non-BAC NSCLC Patients with the Seven Subtypes of UICC6 T4 and M Descriptors that Undergo Revisions as Proposed by IASLC

UICC6 T4 and M Descriptors (IASLC proposed changes)	Total	Deaths	1-yr Survival Estimate (%)	5-yr Survival Estimate (%)	Median Overall Survival (mo)
T4-"additional nodules" (IASLC → T3)	422	250	64.0	22.6	20
T4-"invasion" (IASLC → T4 [no change])	1607	1178	47.4	11.5	12
M-"ipsilateral intra-pulmonary nodules" (IASLC → T4)	745	555	46.2	9.5	11
M-"contralateral intra-pulmonary nodules" (IASLC → M1a)	1148	949	31.1	4.3	7
T4-"pleural dissemination" (IASLC → M1a)	1773	1557	22.7	3.9	5
T4-"pericardial effusion" (IASLC → M1a)	320	282	17.7	3.4	3
M-"distant metastasis" (IASLC → M1b)	6886	6252	18.3	1.3	4

ple comparisons of continuous variables. Univariate survival rate analyses were estimated using the Kaplan and Meier method, with comparisons made between groups by the log-rank test. Cox proportional hazards modeling using time since diagnosis were performed. Each variable in the model was coded using dummy variables. All statistical analyses were conducted using SAS 9.1 statistical software (SAS Institute, Inc., Cary, NC). Statistical significance was assumed for a two-tailed p value less than 0.05.

Ethical Considerations

This research study was approved by the University of California Irvine Institutional Review Board (IRB #2004–3971).

RESULTS

Patients and Tumor Characteristics

About 43,655 incident cases of NSCLC were identified between 1999 and 2003 in CCR, including 2010 BAC patients that were separately analyzed and reported elsewhere.[14] Of the remaining 41,645 non-BAC NSCLC patients, 30,711 (74%) had a histologically confirmed diagnosis. An additional 196 cases where no EOD were available, 997 cases where tumor status were unknown (TXM0), and 5935 cases where nodal status were unknown (NXM0) were excluded. A total of 23,583 patients comprised the final study population for this report used to generate the comparison of the hazard ratio (HR) of the UICC6 and IASLC stages by Cox proportional hazards regression analysis. There were a total of 4122 (17.5%) stage IIIB patients and 8779 (37.2%) stage IV patients. These 12,901 patients comprised the basis for the primary T4 and M descriptor analysis in this report. The median follow-up time for the advanced stage IIIB/IV patients was 9 months (0 to 60 months). Among these IIIB/IV patients, adenocarcinoma (43.2%) was the most frequent tumor histology followed by undifferentiated histology (28.9%), squamous cell carcinoma (22.0%) and large cell carcinoma (5.9%).

Among UICC6 advanced stage IIIB patients, 10.2% had additional nodules in the same lobe, 43.0% had malignant pleural effusion, 7.8% had malignant pericardial effusion, 39.0% were other "T4 invasion." Among UICC6 stage IV patients, 13.1% had ipsilateral intrapulmonary nodules, 8.5% with contralateral pulmonary intrapulmonary nodules, and 78.4% had distant metastasis. The clinicopathologic characteristics of the seven nonoverlapping T4 and M categories were listed in Table 1.

Both "T4-additional nodules" (50.0%) and "ipsilateral intrapulmonary nodules" (48.2%) categories had the highest proportional of adenocarcinoma. Of note, significantly more patients with additional nodules in the same lobe (58.1%) and ipsilateral intrapulmonary nodules (31.0%) underwent surgical than the other five categories. The proportional of patients with unknown histologic grade increased with more advanced disease. Nevertheless, these patients were included in subsequent Cox proportional hazards regression analyses.

External Validation of Univariate Survival Analysis

OS of the Seven Subtypes of UICC6 T4 and M Descriptors that were Reclassified by IASLC Proposed Staging Changes

The 1-year and 5-year survival estimates and median OS of T4 patients due to additional nodules in the same lobe, T4 patients due to malignant pleural dissemination, T4 pa-

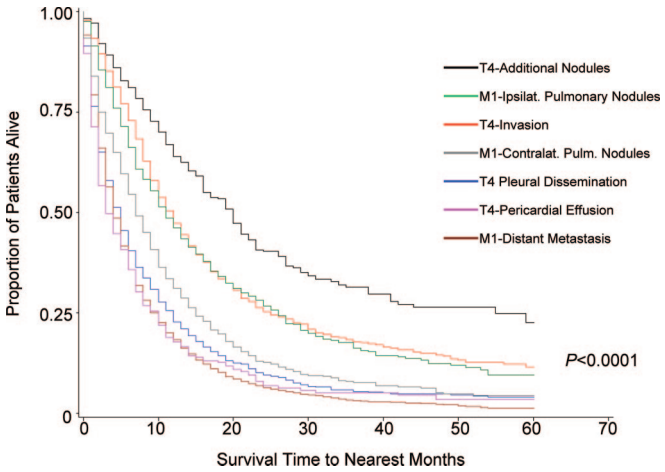

FIGURE 1. Overall survival curves of the 7 subtypes of UICC6 T4 and M descriptors that are reclassified by the proposed IASLC lung cancer staging project.

TABLE 3. Survival Characteristics of non-BAC NSCLC Patients with UICC6 T4 and M Descriptors that Undergo Revisions as Proposed by IASLC Stratified by Individual Histology

UICC6 T4 and M Descriptors (IASLC proposed changes)	Total	Deaths	1-yr Survival Estimate (%)	5-yr Survival Estimate (%)	Median OS (mo)
Adenocarcinoma (N = 5578)					
T4-"additional nodules" (IASLC → T3)	211	117	70.0	25.4	22
T4-"invasion" (IASLC → T4 [no change])	528	370	51.6	12.3	13
M-"ipsilateral intra-pulmonary nodules" (IASLC → T4)	359	254	54.3	12.6	15
M-"contralateral intra-pulmonary nodules" (IASLC → M1a)	487	390	35.6	6.3	8
T4-"pleural dissemination" (IASLC → M1a)	692	592	24.5	5.0	5
T4-"pericardial effusion" (IASLC → M1a)	128	116	14.4	3.0	3
M-"distant metastasis" (IASLC → M1b)	3173	2829	22.2	1.4	5
Squamous cell carcinoma (N = 2834)					
T4-"additional nodules" (IASLC → T3)	97	57	60.0	16.1	17
T4-"invasion" (IASLC → T4 [no change])	571	432	45.8	9.7	11
M-"ipsilateral intra-pulmonary nodules" (IASLC → T4)	196	156	37.0	6.8	8
M-"contralateral intra-pulmonary nodules" (IASLC → M1a)	290	250	27.6	4.5	7
T4-"pleural dissemination" (IASLC → M1a)	503	435	24.3	3.6	5
T4-"pericardial effusion" (IASLC → M1a)	85	77	15.8	—[a]	4
M-"distant metastasis" (IASLC → M1b)	1092	1024	14.7	1.8	4
Large cell carcinoma (N = 761)					
T4-"additional nodules" (IASLC → T3)	19	15	55.7	16.7	12
T4-"invasion" (IASLC → T4 [no change])	74	60	42.8	9.3	9
M-"ipsilateral intra-pulmonary nodules" (IASLC → T4)	28	19	33.8	16.9	7.5
M-"contralateral intra-pulmonary nodules" (IASLC → M1a)	64	57	28.2	2.4	7
T4-"pleural dissemination" (IASLC → M1a)	111	105	14.5	3.1	3
T4-"pericardial effusion" (IASLC → M1a)	25	20	22.3	—[a]	5
M-"distant metastasis" (IASLC → M1b)	440	414	10.6	1.3	3
Undifferentiated carcinoma (N = 3728)					
T4-"additional nodules" (IASLC → T3)	95	61	58.6	15.2	16
T4-"invasion" (IASLC → T4 [no change])	434	316	45.0	15.3	11
M-"ipsilateral intra-pulmonary nodules" (IASLC → T4)	162	126	40.7	5.7	10
M-"contralateral intra-pulmonary nodules" (IASLC → M1a)	307	252	28.1	2.4	7
T4-"pleural dissemination" (IASLC → M1a)	467	425	20.4	2.6	4
T4-"pericardial effusion" (IASLC → M1a)	82	69	24.3	—[b]	3.5
M-"distant metastasis" (IASLC → M1b)	2181	1985	16.2	1.0	4

[a] Data suppressed due to no events after 24 mo.
[b] Data suppressed due to no events after 24 mo.

tients due to malignant pericardial effusion, patients with T4 invasion (IASLC T4), M patients due to ipsilateral intrapulmonary nodules, M patients due to contralateral intrapulmonary nodules, and M patients due to distant metastasis are listed in Table 2. The Kaplan-Mierer survival curves of the seven T4 and M categories are plotted in Figure 1. Identical survival analyses were performed in each of the four histologies: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and undifferentiated carcinoma. The 1-year and 5-year survival estimates and median OS of the seven subtypes of T4 and M descriptor categories stratified by histologies were listed in Table 3. Patients with T4-additional nodules in the same lobe had significantly better survival as a whole and within each histology. On the other hand, patients with malignant pleural dissemination or pericardial effusions had dismal survival.

The survival characteristics (1-year and median OS) of the CCR validation set was compared with the SEER validation set used by IASLC for their external validation exercise and is shown in Table 4. The survival characteristics between the two database sets were very similar and this provides validity to our analysis. Malignant pericardial effusion was not analyzed separately as a category in the IASLC validation set and thus was not shown in Table 4.

OS of Patients with the New IASLC T4 Descriptor, UICC6 T4 (Malignant Pleural Dissemination) Descriptor and UICC6 T4 (Malignant Pericardial Effusion) Descriptor and without Distant Metastasis (M0) According to Nodal Statuses

The 1-year and 5-year survival estimates and median OS of the new IASLC T4 descriptor, UICC6 T4-pleural

TABLE 4. Comparison of Survival Characteristics of the CCR Validation Dataset versus the IASLC SEER Validation Set

	CCR Validation Set		IASLC SEER Validation Set	
	1-yr Survival Estimate (%)	Median Overall Survival (mo)	1-yr Survival Estimate (%)	Median Overall Survival (mo)
T4-"additional nodule in same lobe" (IASLC T3)	64.0	20	59[a]	—
"Ipsilateral Intra-pulmonary nodules" (IASLC T4)	46.2	11	47[a]	11[a]
T4-"invasion" (IASLC T4)	47.4	12	40[b]	10[b]
"Contralateral intra-pulmonary nodules" (IASLC M1a)	31.1	7	31[b]	6[b]
"Pleural dissemination" (IASLC M1a)	22.7	5	21[b]	4[b]
"Distant Metastasis" (IASLC M1b)	18.3	4	15[b]	3[b]

[a] Data from Groome PA, Bolejack V, Crowley JJ, et al. The IASLC lung cancer staging project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage grouping in the forth coming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:694–705.

[b] Data from Postmus PE, Brambilla E, Chansky K, et al. The IASLC lung cancer staging project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. *J Thorac Oncol* 2007;2:686–693.

TABLE 5. Overall Survival of non-BAC NSCLC Patients with "IASLC T4", Pleural Dissemination and Pericardial Effusion without Distant Metastasis According to Nodal Status

Nodal Status	Total	Deaths	1-yr Survival Estimate (%)	5-yr Survival Estimate (%)	Median OS (mo)	*p*
"T4-invasion" (IASLC proposed T4) ($N = 1301$)						
N0	362	246	54.3	14.8	14	<0.0001
N1	126	88	58.8	11.3	16	
N2	707	539	43.6	9.8	11	
N3	106	88	36.5	6.1	9	
Malignant pleural dissemination (IASLC proposed M1a) ($N = 1773$)						
N0	480	398	32.1	6.2	6	<0.0001
N1	73	63	31.6	7.4	6	
N2	1050	945	18.3	2.4	4	
N3	170	151	20.0	4.9	5	
Malignant pericardial effusion (IASLC proposed M1a) ($N = 320$)						
N0	33	26	32.5	7.0	5	0.0461
N1	7	5	28.6	—[a]	7	
N2	206	187	13.8	2.1	3	
N3	74	64	21.8	4.0	5	

[a] Data suppressed due to insufficient events after 10 mo.

dissemination descriptor and UICC6-pericardial effusion descriptors were analyzed and listed in Table 5 and plotted in Figures 2*A–C*, respectively. Although there were statistically significant survival differences among patients with malignant pleural dissemination or pericardial effusion according to the nodal status, the overall dismal survival of these patients justified reclassifying these patients to a M descriptor independent of nodal status (Figures 2*B*, *C*). There were also statistically significant survival differences among patients with T4 invasion according to nodal status and the differences in survival (1-year survival estimate difference of approximately 10% and 5 months improvement in median OS) are large enough to justify reclassifying patients with T4N0-1 from the traditional stage IIIB to stage IIIA. Nevertheless, most of these T4N0-1M0 patients may still not be considered as "resectable" as traditionally considered for IIIA disease.

OS Comparison of Patients with Pericardial Effusion versus Patients with Other M1a Descriptors (Contralateral Intrapulmonary Nodules or Malignant Pleural Dissemination) and M1b Patients

We observed from Tables 2 and 3 that patients with pericardial effusion had dismal survival similar to the IASLC M1b category. The HR of survival of patients with pericardial effusion was compared in a pairwise fashion with other M1a and M1b descriptors and shown in Table 6. Patients with pericardial effusion had statistically significant increased risk of death when compared with other M1a descriptors (contralateral intrapulmonary nodules or malignant pleural dissemination). The HR of patients with pericardial effusion was not statistically significant different from patients with distant metastasis (M1b). Thus, patients with pericardial effusion may be considered as M1b especially if an official subdivi-

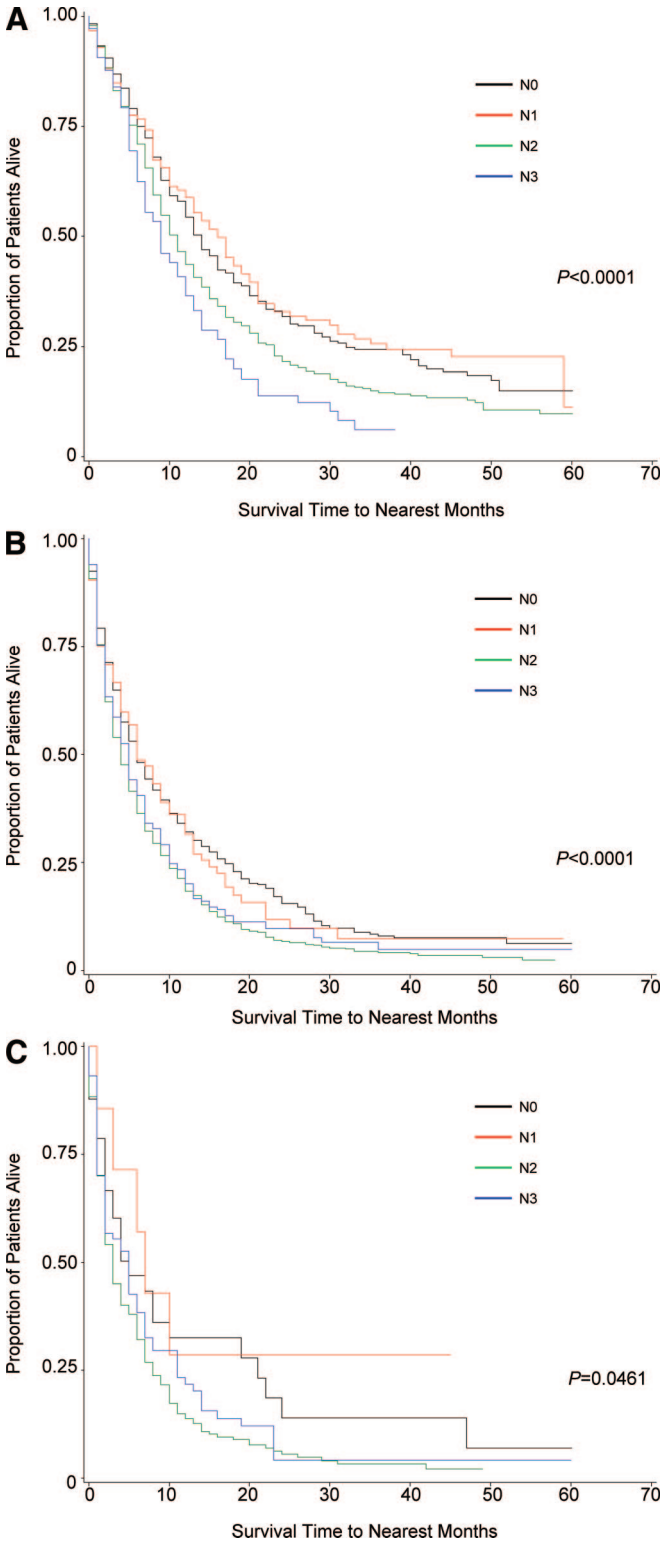

FIGURE 2. *A*, Overall survival curves of "T4-invasion" according to nodal status. *B*, Overall survival curves of "pleural dissemination" according to nodal status. *C*, Overall survival curves of "pericardial effusion" according to nodal status.

TABLE 6. Pairwise Comparison of Hazards Ratio (HR) of Death between Pericardial Effusion and Other IASLC M Descriptors

Pairwise Comparison	HR	95% Confidence Interval	*p*
Malignant pericardial effusion vs. contralateral intrapulmonary nodules	1.453	1.271–1.660	<0.0001
Malignant pericardial effusion vs. malignant pleural dissemination	1.146	1.010–1.302	0.0379
Malignant pericardial effusion vs. distant metastasis (IASLC M1b)	1.032	0.916–1.163	0.6090

sion of stage IV into stage IVA and stage IVB is proposed and adopted.

OS of Stage IA, IB, IIA, IIB, IIIA, IIIB, and IV Patients According to Current (UICC6) and Proposed IASLC Stage Grouping

The reclassification of all the patients in the study (23,583) from the UICC6 stage grouping to IASLC stage grouping were shown in Table 7. The 1-year and 5-year survival estimates and median OS of UICC6 and IASLC staging grouping for stages IA, IB, IIA, IIB, IIIA, IIIB, and IV are listed in Table 8. The survival curves based on the UICC6 and IASLC stage groupings are presented in Figures 3*A*, *B*, respectively. Similarly to the IASLC staging project findings, there was overlap in OS between stage IB and IIA patients in the UICC6 staging system. Survival comparison of advanced staged NSCLC between the CCR validation set and the IASLC SEER validation set is shown in Table 9.

External Multivariate Survival Analysis Validation

Pairwise comparison of the HRs between each stage in the UICC6 and IASLC were performed and the HRs, 95% confidence interval (CI) and *p* value were listed in Table 10. The HRs of the various stages of UICC6 and IASLC proposed staging with stage IA as a referent were determined with Cox proportional hazards analyses after adjusting for multiple independent prognostic factors including age at diagnosis, gender, ethnicity, socioeconomic status, histology, tumor histologic grade, surgery, radiation, and chemotherapy. The HRs, 95% CI and *p*-values of various stages of non-BAC NSCLC as compared with stage I from both UICC6 and IASLC stage are presented in Table 11. The complete list of the HRs, 95% CI and *p*-values of the various prognostic factors from the Cox proportional analyses were listed in supplemental Table 1 (UICC6) and Table 2 (IASLC).

DISCUSSION

The current IASLC proposed changes to the TNM descriptors and stage grouping represents a major and significant change to the staging of lung cancer.[20] The original external validation of these changes was performed using data from SEER between 1998 and 2000.[8] In this report, we

TABLE 7. Reclassifications of All Patients from the UICC6 Stage Grouping to IASLC Stage Grouping

UICC6 Stage Grouping (total)	IASLC Stage Grouping (total)							
	IA (3000)	IB (2573)	IIA (1509)	IIB (1037)	IIIA (3660)	IIIB (1677)	IVA (3241)[a]	IVB (6886)[a]
IA (3000)	3000	—	—	—	—	—	—	—
IB (3430)	—	2573	608	249	—	—	—	—
IIA (338)	—	—	338	—	—	—	—	—
IIB (1383)	—	—	563	607	213	—	—	—
IIIA (2531)	—	—	—	—	2460	71	—	—
IIIB (4122)	—	—	—	181	698	1150	2093	—
IV (8779)	—	—	—	—	289	456	1148	6886

TABLE 8. Comparison of Overall Survival between UICC6 Staging and IASLC Proposed Staging by Various Stages

UICC6						IASLC					
Stage	Total (%)	Deaths	1-yr Survival Estimate (%)	5-yr Survival Estimate (%)	Median Overall Survival (mo)	Stage	Total (%)	Deaths	1-yr Survival Estimate (%)	5-yr Survival Estimate (%)	Median Overall Survival (mo)
Stage IA	3000 (12.7%)	889	87.9	52.0	NR	Stage IA	3000 (12.7%)	889	87.9	52.0	NR
Stage IB	3430 (14.5%)	1370	79.4	42.0	45	Stage IB	2573 (10.9%)	968	82.0	44.1	50
Stage IIA	338 (1.4%)	143	84.4	38.2	41	Stage IIA	1509 (6.4%)	718	76.1	32.6	35
Stage IIB	1383 (5.9%)	771	68.5	26.5	25	Stage IIB	1037 (4.4%)	556	68.4	29.3	25
Stage IIIA	2531 (10.7%)	1704	58.4	14.4	15	Stage IIIA	3660 (15.5%)	2424	58.8	15.9	16
Stage IIIB	4122 (17.5%)	3267	36.3	8.7	8	Stage IIIB	1677 (7.1%)	1305	41.4	8.1	10
Stage V	8779 (37.2%)	7756	22.4	2.4	5	Stage IVA[a]	3241 (13.7%)	2788	25.2	4.1	6
						Stage IVB[a]	6886 (29.2%)	6252	18.3	1.3	4

[a] There is no official stage IVA (M1a) or stage IVB (M1b) as currently proposed by IASLC.
NR, not reached.

adopted all the proposed changes to the T4 and M descriptors and reclassified advanced non-BAC NSCLC according to the new stage grouping and performed a similar validation study using data from the CCR during 1999–2003. We further adopted all the proposed changes to the early T descriptors so as to reclassify the stage all non-BAC NSCLC patients for the Cox proportional hazards regression analysis.

The CCR is the largest contiguous-area population-based cancer registry in the world, collecting over 130,000 of new cancer cases per year in the state of California.[19] California legally mandated cancer reporting in 1988, and standardized data collection procedures and quality control procedures have been in place ever since.[16] Case reporting is estimated at >98% of the entire state of California,[21] and due to data completeness, accuracy, and timeliness, CCR has received the highest level of certification from the North American Association of Central Cancer Registries.[22] All the regional cancer registries in California (Greater California) became part of SEER in 2001. Before 2001, the San Francisco-Oakland regional registry was one of the nine original SEER registries which started in 1973, whereas the San Jose-Monterey and the Los Angeles regional registries became part of SEER in 1992. Thus, there is some overlap and some unique features of using CCR for this validation study when compared with SEER validation set. CCR contains additional data on socioeconomic status and chemotherapy use during the first course of treatment, which are not recorded in SEER. Furthermore, California has an ethnically diverse population with a total population of 35 million thus allowing the inclusion of all major US ethnic groups to be analyzed in the validation study. We have further excluded 10,934 NSCLC cases of cytologically diagnosed specimens as cytology specimens have been shown to be inaccurate in diagnosing NSCLC histology when compared with histologically diagnosed specimens,[17] and 6932 nonmetastatic cases where either the tumor (TX) or the nodal status is unknown (NX). Finally our Cox proportional regression analysis included other known prognostic factors such as histologic grade,[23,24] socioeconomic status,[24,25] and treatment into the analysis. The survival characteristics of the seven subtypes of T4 and M descriptors from the CCR validation set and the IASLC SEER validation set were very similar (Table 4).

Our current study on the stage-specific survival of advanced non-BAC NSCLC using the CCR database essentially agree with the improved prognostication of patients by the IASLC proposed revisions to the T4 and M descriptors. The changes are applicable to non-BAC NSCLC as a whole and within adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or undifferentiated carcinomas. We have performed a separated validation study of the IASLC staging modifications for BAC using the CCR database,[14] since we had previously shown that the survival of BAC has improved

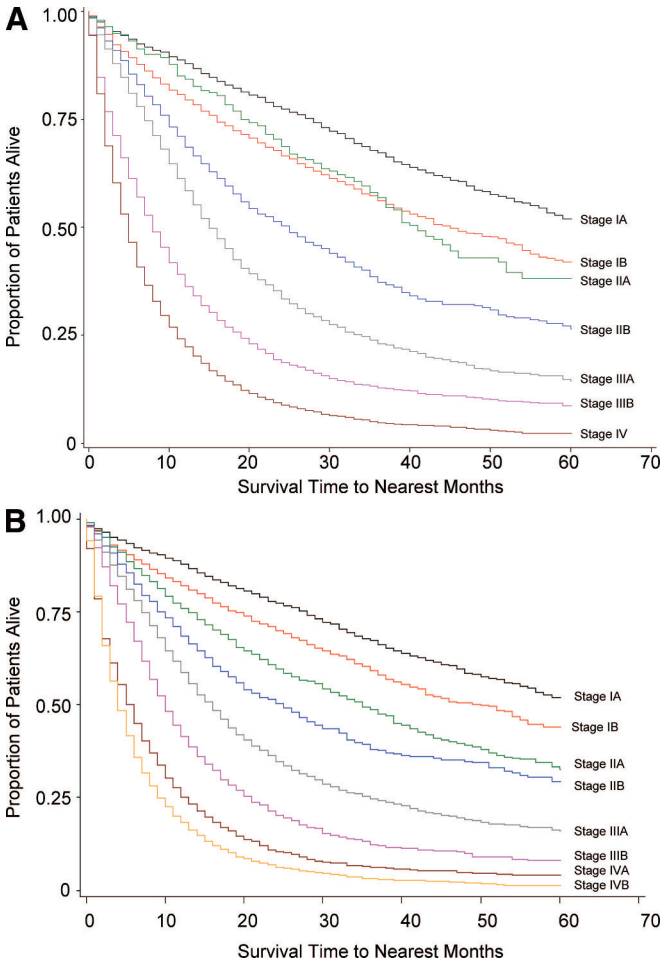

FIGURE 3. *A*, Overall survival curves of individual stage according to the UICC6 stage group. *B*, Overall survival curves of individual stage according to the proposed IASLC stage group.

TABLE 9. Comparison of Median Overall of Advanced Stage non-BAC NSCLC between CCR Validation Set and IASLC SEER Validation Set

	Median Overall Survival (mo)			
	CCR Validation Set		IASLC SEER Validation Set	
	UICC6	IASLC	UICC6	IASLC
Stage IIIA	15	16	14[a]	14[a]
Stage IIIB	8	10	8[a]	9[a]
Stage IV	5	—	4[a]	4[a]
Stage IVA[b]		6		
Stage IVB[b]		4		

[a] Data from Groome PA, Bolejack V, Crowley JJ, et al. The IASLC lung cancer staging project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage grouping in the forth coming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007;2:694–705.

[b] There is no official stage IVA (M1a) and stage IVB (M1b) as proposed by IASLC.

significantly[11] after the publication of the change WHO definition change in BAC[15] and that some of the proposed changes to the T4 and M descriptors had a much more pronounced survival effects in BAC, i.e., T4 due to additional nodules and M due to ipsilateral pulmonary nodules.[9,14]

The current UICC6 T4 descriptor essentially encompasses three different tumor types: mediastinal invasion, satellite nodules, and malignant pleural/pericardial dissemination. We believed IASLC had proposed revisions to the T4 descriptor that successfully separated these three categories. T4 due to additional nodules will be reclassified as T3 in the proposed IASLC revision. As shown in Table 2, the survival of T4 patients due to additional nodules in the same lobe was much better than the rest of the T4 and M descriptor group. This observation is also valid among the individual NSCLC histologies with adenocarcinoma having the best survival time (Table 3). In separate analyses of the SEER database, we have demonstrated that BAC patients with T4 due to additional nodules (T4N0M0) have a median OS of 46 months and a 5-year survival estimate of 45%.[9] Importantly, 72.0% of the patients (T4N0M0) in that study underwent potential curative lobectomy. Among non-BAC NSCLC patients in our SEER analyses, 59% of the T4 (T4N0-2M0) patients with additional nodules in the same lobe had surgical intervention.[10] This indicates that physicians treating NSCLC already consider those T4 patients with additional nodules to have better survival, and that most patients were treated with curative intent. Bryant et al. reported the 5-year survival of 25 (T4-satellite nodules N0M0) patients who were staged by positron emission tomography and underwent complete resection and neo-adjuvant or adjuvant chemotherapy was 57%.[26] Thus reclassifying the T4 descriptor due to additional nodules in the same lobe as T3 is clinically appropriate.[20]

Patients with pleural dissemination (malignant pleural effusion/pleural nodules) in this report had extremely poor survival. Similar to reported in the IASLC staging revision,[4] we reported a 5-year survival rate of 3.1% and median survival of 4 months in patients with pleural dissemination but without distant metastasis in this study. We have also shown that the poor survival of T4 due to pleural dissemination is essentially independent of mediastinal nodal status and thus behaves more like distant metastasis (Table 5 and Figure 2*B*). These patients are considered as "wet IIIB" and treated as stage IV in clinical practice and trials already. Thus reclassifying T4 due to pleural dissemination as M1a codifies what is being practiced in general.

Malignant pericardial effusion is currently staged as T4 in the UICC6 staging but will be reclassified as M1a with the current proposed IASLC revision. The IASLC lung cancer staging project did not separately analyze malignant pericardial effusion from malignant pleural effusion within the current T4 descriptor. In this report, we showed that isolated pericardial effusion is much less common than isolated pleural dissemination in advanced lung cancer. We also showed that median survival of patients with even isolated pericardial effusion without distant metastasis was dismal with a median survival time of 3 months and 5-year survival estimate of 3.4%. This dismal 3-month median survival time is consistent

TABLE 10. Pairwise Comparisons of Hazard Ratio of UICC and IASLC Stages

	Hazard Ratio		*p*	
Comparisons	**UICC6**	**IASLC**	**UICC6**	**IASLC**
IB vs. IA	1.465 (1.347–1.594)	1.337 (1.221–1.465)	<0.0001	<0.0001
IIA vs. IB	0.996 (0.838–1.183)	1.369 (1.243–1.508)	0.9612	<0.0001
IIB vs. IIA	1.639 (1.371–1.960)	1.267 (1.134–1.415)	<0.0001	<0.0001
IIIA vs. IIB	1.481 (1.360–1.613)	1.467 (1.338–1.609)	<0.0001	<0.0001
IIIB vs. IIIA	1.623 (1.530–1.721)	1.516 (1.417–1.622)	<0.0001	<0.0001
IV vs. IIIB	1.461 (1.403–1.523)	1.770 (1.669–1.876)	<0.0001	<0.0001

TABLE 11. Comparison of Hazards Ratio of Stage According to UICC6 and IASLC Proposed Staging System Using Cox Proportional Hazards Regression Analysis

UICC6				IASLC			
Stage	**Hazards Ratio[a]**	**95% Confidence Interval**	***p***	**Stage**	**Hazards Ratio[a]**	**95% Confidence Interval**	***p***
Stage IA	1.00			Stage IA	1.00		
Stage IB	1.414	(1.300–1.539)	<0.0001	Stage IB	1.301	(1.188–1.426)	<0.0001
Stage IIA	1.607	(1.347–1.918)	<0.0001	Stage IIA	1.908	(1.729–2.107)	<0.0001
Stage IIB	2.525	(2.291–2.784)	<0.0001	Stage IIB	2.360	(2.120–2.626)	<0.0001
Stage IIIA	2.798	(2.566–3.050)	<0.0001	Stage IIIA	3.004	(2.767–3.261)	<0.0001
Stage IIIB	3.686	(3.396–4.002)	<0.0001	Stage IIIB	3.681	(3.346–4.048)	<0.0001
Stage IV	5.246	(4.844–5.682)	<0.0001	Stage IVA[b]	4.897	(4.493–5.338)	<0.0001
				Stage IVB[b]	6.842	(6.296–7.436)	<0.0001

[a] Adjusted for age, gender, ethnicity, socioeconomic status, histology, histologic grade, surgery, radiation, and chemotherapy. Refer to supplemental tables for the full Cox models.
[b] There is no official stage IVA (M1a) or stage IVB (M1b) as currently proposed by IASLC.

with survival reported in other studies of patients with pericardial effusion who underwent surgical pericardial window for drainage.[27,28] This poor survival is essentially independent of mediastinal lymph node status (Table 5 and Figure 2*C*). In fact, the survival of patients with pericardial effusion is closer to M1b patients in our report than M1a patients. In pairwise comparisons, the HR of patients with pericardial effusion was significantly worse than patients with other M1a classifications such as contralateral intrapulmonary nodules or malignant pleural dissemination but not statistically different from patients with M1b disease (Table 6). Thus consideration should be given to classify pericardial effusion as M1b rather than M1a especially if there is going to be an official subdivision of stage IV into stage IVA and stage IVB.

Similar to a previous analysis of the SEER database,[10] in this report patients with M descriptor due to ipsilateral intrapulmonary nodules had significantly better survival among stage IV patients and similar survival to other "T4 invasion" patients (12 months median OS). This survival advantage is again observed with each individual histology (Table 3). Thus it is appropriate to reclassify M descriptor due to ipsilateral pulmonary nodules as T4. In our previous analysis using SEER database,[9] BAC patients with ipsilateral intrapulmonary nodules had a median survival of 20 months, which is superior to the 15 months median survival observed for adenocarcinoma in this report. Again a majority of the BAC patients with ipsilateral pulmonary nodules (67.5%) in our previous report underwent surgical treatment and those patients had significantly prolonged survival.[9] Nagai et al. reported a 5-year survival of 42.1% in patients who under surgical resection with intrapulmonary metastasis in different lobes without mediastinal nodal metastasis.[29] In this report, 31% of the M patients with ipsilateral intrapulmonary nodules had surgical treatment (Table 1). Again these data indicate that physicians are already treating a fair amount of such patients with curative intent. Thus reclassifying patients with ipsilateral pulmonary nodules from M to T4 makes eminent clinical sense and is consistent with what is being practiced in the community.

We adopted all the IASLC proposed T and M descriptors changes and reclassified UICC6 stages IA, IB, IIA, IIB, IIIA, IIIB, and IV into the new IASLC proposed stages IA, IB, IIA, IIB, IIIA, IIIB, IVA, and IVB for the Cox proportional hazards regression analysis. Similar to the IASLC stage grouping analysis,[7] there was no significant prognostic significance between stage IB and IIA in the UICC6 clinical staging system. The proposed IASLC stage grouping also allows better separation of stage IB and IIA than UICC6 staging in our analysis (Tables 10 and 11). Furthermore, the HRs for death continue to increase from stage IVA (versus stage IA; HR = 4.90) to stage IVB (versus stage IA; HR = 6.84) indicating that subdividing M descriptor into M1a and M1b are justifiable even though the survival time for both M1a and M1b patients are poor.[30]

One of the significant but potentially controversial proposed IASLC stage grouping change is to down stage T4N0-1M0 from the current UICC6 stage IIIB to stage IIIA. Stage IIIA NSCLC is generally considered to be resectable whereas stage IIIB is generally considered to be unresectable, although there are exceptions to this conceptual categorization. The 5-year survival estimate and median survival of the IASLC proposed T4N0M0 (14.8% and 14 months) and T4N1M0 (11.3% and 16 months) (Table 5) were closer to UICC6 stage IIIA (14.4% and 15 months, Table 8) than UICC stage IIIB (8.7% and 8 months, Table 8). A review of published series on radical resection of T4 (trachea, carina, left atrial, aortic, vena caval, or vertebral body invasion) lung cancer with minimal nodal involvement reported a median survival of 19 months and 5-year survival of 31%.[31] Thus the survival time analysis justifies moving T4N0-1M0 to stage IIIA. Nonetheless, the current concept that stage IIIA NSCLC represents resectable disease may be challenged in the future if tumors that invade vertebral bodies, heart, pericardium, major vessels with minimal mediastinal lymph node involvement are staged as IIIA since the multidisciplinary surgical skills required for radical resection of "T4 invasion" tumors are not often available. Furthermore, practice guidelines will have to be updated accordingly.[32]

This study is retrospective in nature and thus carried with it limitations of population-based studies. There was no uniform standard protocol on how the lung cancer patients were staged (i.e., lymph node staging or systemic staging), thus all the CCR registry patients were analyzed using "best available stage" based on combined clinical and pathologic staging data. A large number of cases were not analyzed due to unknown histology, nodal status, or T-descriptor, thus limiting our ability to generalize these findings to all non-BAC NSCLC patients. There was no centralized review of pathologic specimens. Nevertheless, the accuracy of NSCLC histologic reporting in SEER has been reported favorably in comparison to independent review.[33] There is no uniform protocol on how treatment (surgery, radiation, or chemotherapy) was given. Despite these limitations, our pairwise comparison of survival characteristics of advanced NSCLC of our CCR validation set is very similar to the IASLC SEER validation set. Moreover, we have included many independent prognostic factors into the Cox proportional regression analysis.

In summary, the proposed staging changes reflect a better prognostication of advanced stage IIIB and stage IV NSCLC. Nevertheless, the survival of stage IIIB and stage IV NSCLC regardless of current or proposed staging system remains very poor. Future molecular tumor classifications, lung cancer screening trial evaluations, and increased advocacy of lung cancer research are critically needed.

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